## 1. THE OBJECTIONS UNDER 37 C.F.R. §1.75(c) SHOULD BE WITHDRAWN

Claims 2-3, 19, 34 and 35 are objected under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 2-3, 34, and 35 have been canceled and Claim 19 has amended to be dependent from Claim 4. Thus, the Examiner's objection has been obviated.

## 2. THE REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claims 1-6, 27, 33, 39, 46, and 47 are rejected under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. The Examiner contends that the specification provides no guidance as to how to obtain cell-specific regulatory elements other than the hypersensitive sites I-IV associated with the human globin gene cluster, which are sufficiently small in size to be used with a coding sequence in adeno-associated virus ("AAV"). This rejection should be withdrawn for the reasons detailed below.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. U.S. v. Telectronics, Inc. 857 F. 2d 778, 8 USPQ 2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1384 (Fed. Cir. 1986). The need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. §112. The dispositive issue is whether the disclosure would have enabled one of ordinary skill in the art to practice the invention without undue experimentation. In re Strahilevitz, 212 U.S.P.Q. 561, 563 (CCPA 1982). The focus is not on whether experimentation would be required, but whether such experimentation is undue. In analyzing this very issue, the Court of Appeals for the Federal Circuit ("CAFC") determined that experimentation, though laborious, is not undue experimentation where the specification provides a reasonable amount of guidance. In re Wands 858 F. 2d 731 (Fed. Cir. 1988). In the present instance, the specification provides one of ordinary skill in the art with sufficient guidance to meet the requirements of Section 112. Therefore, as explained below, the claimed invention is enabled within the meaning of Section 112.

Applicants respectfully assert that the specification teaches recombinant AAV vectors comprising nucleic acid sequences encoding gene products under the control of cell-specific *cis*-acting regulatory sequences other than the hypersensitive sites I-IV associated with the human globin gene cluster. For example, the specification discloses recombinant AAV vectors comprising nucleic acid sequences encoding Factor IX under the control of a liver specific promoter (see page 22, lines 18-27). The specification states that "[t]he skilled artisan is limited only in the ability to find an appropriate *cis*-acting regulatory element to confer proper expression within the target cell." At the time of the June 3, 1992 effective date of the instant application[1/], numerous cell-specific and tissue-specific regulatory elements were known to those of skill in the art, *e.g.*, the insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315:115-122), the immunoglobulin gene control region which is active in lymphoid cells (Grosschedl et al., 1984, Cell 38:647-658; Adames et al., 1985, Nature 318:533-538; Alexander et al., 1987, Mol. Cell. Biol. 7:1436-1444), the myelin basic protein gene control region which is active in oligodendrocyte cells in the brain (Readhead et al., 1987, Cell 48:703-712) and the myosin light chain-2 gene control region which is active in skeletal muscle (Sani, 1985, Nature 314:283-286). Further, at the time of the invention one skilled in the art would have known that AAV vectors were (and are) only capable of packaging about 4,000-5,000 bases of DNA (see, *e.g.*, page 485 of LaFace et al., 1988, Virology 162:483-485). Thus, the instant specification provides ample guidance to the skilled artisan to make and obtain the recombinant AAV vectors of the present invention. Accordingly, Applicants submit that the pending claims are fully enabled for the scope of the recited subject matter and, respectfully request that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

### 3. THE CLAIMS ARE NOT ANTICIPATED BY U.S. PATENT NO. 5,252,479

Claims 1-16, 20-29, and 46-47 are rejected under 35 U.S.C. § 102 (e) as anticipated by U.S. Patent No. 5,252,479 ("'479 patent"). The Examiner directs the Applicants' attention to Example 6 of the '479 Patent. For the reasons detailed below, Applicants respectfully request that this rejection be withdrawn.

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[1/] The present application is a continuation of a series of applications, the earliest of which was filed June 3, 1992.



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Applicants have canceled Claims 2, 3, 5, 6, 13-15, and 22-24, and amended Claims 1, 9, 10, 12, 16, 21, 27, 46 and 47 to more particularly point out and distinctly claim the invention. In particular, independent Claims 1 and 27, as amended, recite a recombinant AAV vector comprising a eukaryotic nucleic acid sequence encoding a wild-type gene product controlled by a eukaryotic based *cis*-acting regulatory element heterologous to the wild-type gene product. Example 6 of the '479 Patent merely teaches a recombinant AAV vector consisting of the β-globin gene under the control of a portion of the β-globin gene's native regulatory element. The '479 Patent does not disclose eukaryotic nucleic acid sequences encoding wild-type gene products under the control of eukaryotic cell-specific *cis*-acting regulatory elements heterologous to the wild-type gene product. The legal test for anticipation under 35 U.S.C. § 102 requires that the prior art meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The '479 Patent does not meet every element of the claimed invention. Therefore, a recombinant AAV vector of the present invention is not anticipated by the '479 Patent.

In view of the foregoing amendments and remarks, Applicants submit that the rejections under 35 U.S.C. § 102 (e) should be withdrawn.

## 4. THE CLAIMS ARE NEITHER ANTICIPATED NOR MADE OBVIOUS BY WALSH I

### 4.1. THE CLAIMS ARE NOT ANTICIPATED BY WALSH I

Claims 1-29, 46, and 47 are rejected under 35 U.S.C. § 102 (b) as anticipated by Walsh et al., 1991, J. Clin. Res. 39(2):325A ("Walsh I"). The Examiner contends that Walsh I is silent regarding whether or not the transcriptional marker had any affect on the gene product encoded by the vector. Thus, the Examiner concludes that a recombinant AAV vector comprising a nucleic acid sequence encoding a wild-type gene product under the control of a *cis*-acting regulatory element is anticipated by Walsh I. For the reasons detailed below, Walsh I does not anticipate the claimed invention.

Applicants have canceled Claims 2, 3, 5, 6, 13-15, 18, and 22-24 and amended Claims 1, 9, 10, 12, 16, 17, 19, 21, 27, 46, and 47 to more particularly point out and distinctly claim the invention. In particular, independent Claims 1 and 27 have been amended to recite recombinant AAV vectors comprising a eukaryotic nucleic acid sequence encoding a wild-

type gene product under the control of eukaryotic *cis*-acting regulatory sequence heterologous to the wild-type gene product. Walsh I merely discloses recombinant AAV vectors consisting of a globin gene under the control of a portion of the regulatory element native to the globin gene. Walsh I does not teach recombinant AAV vectors comprising a eukaryotic nucleic acid sequence encoding a wild-type gene product under the control of eukaryotic *cis*-acting regulatory sequence heterologous to the wild-type gene product. Thus, Walsh I does not meet every element of claimed invention and therefore, does not anticipate the claimed invention.

In view of the foregoing, the rejections under 35 U.S.C. § 102 (b) should be withdrawn.

### 4.2. WALSH I DOES NOT RENDER THE CLAIMED INVENTION OBVIOUS

Claims 1-29, 46, and 47 are rejected under 35 U.S.C. § 103 (a) as obvious over Walsh I. The Examiner contends that in view of Walsh a recombinant AAV vector comprising a nucleic acid sequence encoding a wild-type gene product under the control of a *cis*-acting regulatory element would have been obvious.

Claims 30-35 and 39 encompassing the recombinant AAV vectors of the invention encoding FACC protein and Factor IX protein, respectively, are rejected under 35 U.S.C. § 103 (a) as obvious over Walsh I. The Examiner contends that it would have been obvious in view of Walsh I to use the entire locus control region ("LCR") to control the expression of the globin gene and to substitute the Factor IX gene for the globin gene to overcome deficiencies in Factor IX.

Applicants have canceled Claims 2, 3, 5, 6, 13-15, 18, 22-24, 32, 34, and 35 and amended Claims 1, 9, 10, 12, 16, 17, 19, 21, 27, 31, 46, and 47 to more particularly point out and distinctly claim the invention. The claims, as amended, cover the AAV vectors of the invention in which the wild-type eukaryotic gene is controlled by a *cis*-acting eukaryotic promoter heterologous to the eukaryotic gene. Nothing in Walsh I suggests recombinant AAV vectors comprising a wild-type gene product under the control of eukaryotic *cis*-acting regulatory sequence heterologous to the wild-type gene product. There is no motivation in Walsh I to replace the globin gene with the Factor IX gene. The purpose in Walsh I was to express the globin gene under the control of a portion of the native globin gene regulatory elements to ensure high levels of expression of the globin gene in erythroid cells. The



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Examiner is trying to supply a motivation to replace the globin gene with the Factor IX gene based on the improper use of hindsight. Since obviousness requires the suggestion and the reasonable expectation of success, Walsh I does not render the claimed invention obvious. Therefore, the rejections under 35 U.S.C. § 103 should be withdrawn.

## 5. CLAIMS 33-35 ARE NOT ANTICIPATED BY WALSH II

Claims 33-35 are rejected under 35 U.S.C. § 102 (b) as anticipated by Walsh et al., 1993, Blood 82 (10 Suppl. 1):347a ("Walsh II"). The Examiner contends that all of the claim limitations of Claims 33-35 are disclosed by Walsh II.

As stated above, the legal test for anticipation under 35 U.S.C. § 102 requires that the prior art meet every element of the claimed invention, and that such a determination is one of fact. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Thus, Walsh II does not anticipate the methods of the claimed invention.

Applicants have canceled Claims 34 and 35, without prejudice. Claim 33 is directed to recombinant AAV vectors comprising the nucleic acid sequence encoding wild-type Fanconi anemia C complementing ("FACC") protein under the control of eukaryotic *cis*-acting regulatory sequence heterologous to the wild-type FACC protein. Walsh II merely describes a recombinant AAV consisting of a FACC gene linked to a viral promoter that allows for correction in CD34+ hematopoietic cells. Thus, Walsh II does not meet every element of claimed invention. According, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (b) be withdrawn.

## CONCLUSION

Applicants respectfully request consideration and entry of the foregoing amendments

and remarks. It is believed that the application is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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Enclosure



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